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L2 46498 VEGF

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L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
2003:275911 Document No. 139:95567 A set of loop-1 and -3 structures in the novel vascular endothelial growth factor (**VEGF**) family member, **VEGF**-ENZ-7, is essential for the activation of VEGFR-2 signaling. Kiba, Atsushi; Yabana, Naoyuki; Shibuya, Masabumi (Institute of Medical Science, Division of Genetics, University of Tokyo, 4-6-1 Shirokane-dai, Minato-ku, Tokyo, 108-8639, Japan). Journal of Biological Chemistry, 278(15), 13453-13461 (English) 2003. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB The vascular endothelial growth factor (**VEGF**) family plays important roles in angiogenesis and vascular permeability. Novel members of the **VEGF** family encoded in the Orf virus genome, **VEGF** -E, function as potent angiogenic factors by specifically binding and activating VEGFR-2 (KDR). **VEGF**-E is about 45% homologous to **VEGF**-A at amino acid levels, however, the amino acid residues in **VEGF**-A crucial for the VEGFR-2-binding are not conserved in **VEGF**-E. To understand the mol. basis of the biol. activity of **VEGF**-E, the authors have functionally mapped residues important for interaction of **VEGF**-E with VEGFR-2 by exchanging the domains

between **VEGF**-ENZ-7 and PlGF, which binds only to VEGFR-1 (Flt-1). Exchange on the amino- and C-terminal regions had no suppressive effect on biol. activity. However, exchange on either the loop-1 or -3 region of **VEGF**-ENZ-7 significantly reduced activities. Introduction of the loop-1 and -3 of **VEGF**-ENZ-7 to placenta growth factor rescued the biol. activities. The chimera between **VEGF**-A and **VEGF**-ENZ-7 gave essentially the same results. These findings strongly suggest that a common rule exists for VEGFR-2 ligands (**VEGF**-ENZ-7 and **VEGF**-A) that they build up the binding structure for VEGFR-2 through the appropriate interaction between loop-1 and -3 regions.

L4 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 1

1998035455. PubMed ID: 9351807. The crystal structure of vascular endothelial growth factor (**VEGF**) refined to 1.93 A resolution: multiple copy flexibility and receptor binding. Muller Y A; Christinger H W; Keyt B A; de Vos A M. (Department of Protein Engineering, Genentech, Inc., South San Francisco, CA 94080, USA.) Structure (London, England), (1997 Oct 15) 5 (10) 1325-38. Journal code: 9418985. ISSN: 0969-2126. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Vascular endothelial growth factor (**VEGF**) is an endothelial cell-specific angiogenic and vasculogenic mitogen. **VEGF** also plays a role in pathogenic vascularization which is associated with a number of clinical disorders, including cancer and rheumatoid arthritis. The development of **VEGF** antagonists, which prevent the interaction of **VEGF** with its receptor, may be important for the treatment of such disorders. **VEGF** is a homodimeric member of the cystine knot growth factor superfamily, showing greatest similarity to platelet-derived growth factor (PDGF). **VEGF** binds to two different tyrosine kinase receptors, kinase domain receptor (KDR) and Fms-like tyrosine kinase 1 (Flt-1), and a number of **VEGF** homologs are known with distinct patterns of specificity for these same receptors. The structure of **VEGF** will help define the location of the receptor-binding site, and shed light on the differences in specificity and cross-reactivity among the **VEGF** homologs. RESULTS: We have determined the crystal structure of the receptor-binding domain of **VEGF** at 1.93 A resolution in a triclinic space group containing eight monomers in the asymmetric unit. Superposition of the eight copies of **VEGF** shows that the beta-sheet core regions of the monomers are very similar, with slightly greater differences in most loop regions. For one loop, the different copies represent different snapshots of a concerted motion. Mutagenesis mapping shows that this loop is part of the receptor-binding site of **VEGF**. CONCLUSIONS: A comparison of the eight independent copies of **VEGF** in the asymmetric unit indicates the conformational space sampled by the protein in solution; the root mean square differences observed are similar to those seen in ensembles of the highest precision NMR structures. Mapping the receptor-binding determinants on a multiple sequence alignment of **VEGF** homologs, suggests the differences in specificity towards KDR and Flt-1 may derive from both sequence variation and changes in the flexibility of **binding loops**. The structure can also be used to predict possible receptor-binding determinants for related cystine knot growth factors, such as PDGF.

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

1996:548535 Document No. 125:215688 Ribozymes with RNA protein-binding site and ribozyme domain loop conformation. Burke, John M.; Sargueil, Bruno (University of Vermont and State Agricultural College, USA). PCT Int. Appl. WO 9621730 A2 19960718, 55 pp. DESIGNATED STATES: W: AU, CA, JP, MX; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US16882 19951227. PRIORITY: US 1995-371986 19950113.

AB This invention includes ribozymes having a ligand-binding site formed as a

double-stranded RNA and a single-stranded loop. The ribozymes have enzymic activity to cleave and/or ligate themselves or sep. RNA mols. Especially ribozyme protein-binding sites are studied. Recombinant ribozymes can be usefully expressed in cells.

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L5 1681 L2 AND VEGF-C

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L6 36 L5 AND LOOP

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L7 11 DUP REMOVE L6 (25 DUPLICATES REMOVED)

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L7 ANSWER 1 OF 11 MEDLINE on STN DUPLICATE 1
2003194939. PubMed ID: 12714608. EMAP-II expression is associated with macrophage accumulation in primary uveal melanoma. Clarijs Ruud; Schalkwijk Lia; Ruiter Dirk J; de Waal Robert M W. (Department of Pathology, University Medical Centre, Nijmegen, The Netherlands.. r.clarijs@pathol.umcn.nl) . Investigative ophthalmology & visual science, (2003 May) 44 (5) 1801-6. Journal code: 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.
AB PURPOSE: Primary uveal melanoma may contain arcs, **loops**, and networks of periodic acid-Schiff (PAS)-positive patterns, along which numerous macrophages are present. Their recruitment into tumor tissue is mediated by chemotactic cytokines, for which vascular endothelial growth factor (**VEGF**)-**C** and endothelial monocyte-activating polypeptide ((EMAP)-II are candidates. In this study, the extent of **VEGF-C** and EMAP-II immunoreaction was related to infiltration of macrophages. METHODS: Serial sections of 25 primary uveal melanoma lesions were analyzed by immunohistochemistry. RESULTS: The analysis showed no correlation of **VEGF-C** immunoreaction and localization of macrophages. However, accumulation of macrophages occurred at sites of EMAP-II expression, especially in areas containing nests of tumor cells, surrounded by arcs, **loops**, and network patterns. In tumors with a strong EMAP-II immunoreaction, the adhesion molecule intracellular adhesion molecule (ICAM)-1 was strongly expressed on endothelial cells. EMAP-II-positive endothelial cells did not express **VEGF** receptor-2. However, extensive release of von Willebrand factor was observed. Signs of apoptosis were found neither in tumor cells nor endothelial cells. CONCLUSIONS: In uveal melanoma, macrophages accumulate at sites of EMAP-II expression. Based on the results, it may be hypothesized that this process of chemotaxis is facilitated by EMAP-II-dependent expression of ICAM-1 on vascular endothelial cells and concomitantly leads to localized vascular damage, as indicated by release of von Willebrand factor.

L7 ANSWER 2 OF 11 MEDLINE on STN DUPLICATE 2
2003083002. PubMed ID: 12594815. Malignant mesothelioma growth inhibition by agents that target the **VEGF** and **VEGF-C** autocrine **loops**. Masood Rizwan; Kundra Ajay; Zhu SuTao; Xia Guangbin; Scalia Pierluigi; Smith D Lynne; Gill Parkash S. (Department of Pathology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA.. masood@usc.edu) . International journal of cancer. Journal international du cancer, (2003 May 1) 104 (5) 603-10. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.
AB Malignant mesothelioma (MM) is a locally aggressive tumor that originates from the mesothelial cells of the pleural and sometimes peritoneal

surface. Conventional treatments for MM, consisting of chemotherapy or surgery give little survival benefit to patients, who generally die within 1 year of diagnosis. Hence, there is an urgent need for the development of alternative therapies. Vascular endothelial growth factor (**VEGF**) is an autocrine growth factor for MM. The closely related molecule, **VEGF-C**, is also implicated in malignant mesothelioma growth. **VEGF-C** and its cognate receptor VEGFR-3 are co-expressed in mesothelioma cell lines. A functional **VEGF-C** autocrine growth **loop** was demonstrated in mesothelioma cells by targeting **VEGF-C** expression and binding to VEGFR-3. The ability of novel agents that reduce the levels of **VEGF** and **VEGF-C** to inhibit mesothelioma cell growth in vitro was assessed. Antisense oligonucleotide (ODN) complementary to **VEGF** that inhibited **VEGF** and **VEGF-C** expression simultaneously specifically inhibited mesothelioma cell growth. Similarly, antibodies to **VEGF** receptor (VEGFR-2) and **VEGF-C** receptor (VEGFR-3) were synergistic in inhibiting mesothelioma cell growth. In addition, a diphtheria toxin-**VEGF** fusion protein (DT-**VEGF**), which is toxic to cells that express **VEGF** receptors was very effective in inhibiting mesothelioma cell growth in vitro. These results indicate that targeting **VEGF** and **VEGF-C** simultaneously may be an effective therapeutic approach for malignant mesothelioma.

L7 ANSWER 3 OF 11 MEDLINE on STN DUPLICATE 3

2003092551. PubMed ID: 12604407. A paracrine **loop** in the vascular endothelial growth factor pathway triggers tumor angiogenesis and growth in multiple myeloma. Vacca Angelo; Ria Roberto; Ribatti Domenico; Semeraro Fabrizio; Djonov Valentin; Di Raimondo Francesco; Dammacco Franco. (Department of Biomedical Sciences and Human Oncology, University of Bari Medical School, Italy.. avacca@dimo.uniba.it) . Haematologica, (2003 Feb) 88 (2) 176-85. Journal code: 0417435. ISSN: 0390-6078. Pub. country: Italy. Language: English.

AB BACKGROUND AND OBJECTIVES: In tumors, vascular endothelial growth factor-A (**VEGF**-A) stimulates angiogenesis and vascular permeability by activating the tyrosine kinase receptor-2 (VEGFR-2 or KDR/Flk-1) and-1 (VEGFR-1 or Flt-1). DESIGN AND METHODS: The distribution and function of **VEGF** homologs and their receptors on bone marrow plasma cells, endothelial cells, and other stromal cells (residual stromal cells) were examined in patients with multiple myeloma (MM). RESULTS. Plasma cells secrete **VEGF**-A (and **VEGF**-B, **VEGF-C** and **VEGF**-D, albeit marginally) into their conditioned medium (CM). CM **VEGF**-A stimulates proliferation and chemotaxis in endothelial cells (both being mandatory for angiogenesis) via **VEGF** receptor-2 (VEGFR-2), and in residual stromal cells via the VEGFR-1. Residual stromal cells secrete **VEGF-C** and **VEGF** -D, but little of the other homologs. Their CM **VEGF-C** and **VEGF**-D increase in response to plasma cell CM and trigger plasma cell proliferation via VEGFR-3. Proliferation in all cell types parallels VEGFR and extracellular signal-regulated protein kinase-2 (ERK-2) phosphorylation. The homologs and receptors are weakly or inconstantly expressed in patients with monoclonal gammopathies of undetermined significance or vitamin B12/iron deficiency anemias. INTERPRETATION AND CONCLUSIONS: This study shows that the **VEGF** pathway is directly involved in tumor angiogenesis and growth in MM. A paracrine **VEGF loop** for MM progression is suggested. This, in turn, provides a further indication that the **VEGF** pathway and its signaling proteins may be appropriate targets in the management of MM.

L7 ANSWER 4 OF 11 MEDLINE on STN DUPLICATE 4

2002145239. PubMed ID: 11877295. Vascular endothelial growth factor (**VEGF**)-**C** signaling through FLT-4 (VEGFR-3) mediates leukemic cell proliferation, survival, and resistance to chemotherapy. Dias Sergio; Choy Margaret; Alitalo Kari; Rafii Shahin. (Division of Hematology/Oncology, Weill Medical College of Cornell University, 1300 York Ave, New York, NY 10021, USA.) Blood, (2002 Mar 15) 99 (6) 2179-84. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Similar to solid tumors, growth of leukemias may also be angiogenesis dependent. Furthermore, tyrosine kinase receptors specific to endothelial cells are expressed on certain subsets of leukemias. We have previously demonstrated the existence of a **VEGF**/VEGFR-2 autocrine **loop** on leukemic cells that supports their growth and migration. Here, we demonstrate that in response to leukemia-derived proangiogenic and proinflammatory cytokines such as basic fibroblast growth factor and IL-1, endothelial cells release increasing amounts of another vascular endothelial growth factor (**VEGF**) family member, **VEGF-C**. In turn, interaction of **VEGF-C** with its receptor VEGFR-3 (FLT-4) promotes leukemia survival and proliferation. We demonstrate in 2 cell lines and 5 FLT-4(+) leukemias that **VEGF-C** and a mutant form of the molecule that lacks the KDR-binding motif induce receptor phosphorylation, leukemia proliferation, and increased survival, as determined by increased Bcl-2/Bax ratios. Moreover, **VEGF-C** protected leukemic cells from the apoptotic effects of 3 chemotherapeutic agents. Because most leukemic cells release proangiogenic as well as proinflammatory cytokines, our data suggest that the generation of a novel paracrine angiogenic **loop** involving **VEGF-C** and FLT-4 may promote the survival of a subset of leukemias and protect them from chemotherapy-induced apoptosis. These results identify the **VEGF-C**/FLT-4 pathway as a novel therapeutic target for the treatment of subsets of acute leukemia.

L7 ANSWER 5 OF 11 MEDLINE on STN DUPLICATE 5

2002258616. PubMed ID: 11999550. Angiogenic and lymphangiogenic molecules in hematological malignancies. Orpana Arto; Salven Petri. (Department of Clinical Chemistry, Helsinki University Central Hospital, Finland.) Leukemia & lymphoma, (2002 Feb) 43 (2) 219-24. Ref: 79. Journal code: 9007422. ISSN: 1042-8194. Pub. country: Switzerland. Language: English.

AB In this review, the role of angiogenic and lymphangiogenic growth factors in hematological malignancies is summarized, alongside with possible therapeutic applications. Recent data demonstrate the importance of angiogenesis in hematologic malignancies including leukemia, lymphoma, and multiple myeloma. Expression of angiogenic polypeptides vascular endothelial growth factor (**VEGF**) and basic fibroblast growth factor (bFGF) associate with clinical characteristics in human leukemia and lymphoma, and their serum concentrations serve as predictors of poor prognosis. **VEGF** and **VEGF-C** also act as survival factors on leukemia. Furthermore, certain hematological malignancies both produce angiogenic or lymphangiogenic growth factors including **VEGF** and **VEGF-C**, and also express their receptors, resulting in the generation of autocrine **loops** that may support cancer cell survival and proliferation. Inhibition of the action of key regulators of endothelial cell growth, alone or in combination with other antiangiogenic drugs and/or established chemo- or immunotherapy regimens, is a potential target for therapeutic intervention in hematological malignancies.

L7 ANSWER 6 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 6

2003029382 EMBASE Participation of hepatocyte growth factor (HGF) and MET autocrine/paracrine **loop** in liver metastasis of gastric cancer. Yonemura Y.; Endo Y.; Bandou E.; Kawamura T.; Kinoshita K.; Takahashi S.;

Sugiyama K.; Sasaki T.. Y. Yonemura, Surg. Department of Gastric Cancer, Shizuoka Cancer Center, Suntou-Gun, Nagaizumi-Machi, Shizuoka-Ken 411-0934, Japan. y.yonemura@scchr.jp. Experimental Oncology 24/2 (89-98) 2002.
Refs: 36.
ISSN: 0204-3564. CODEN: EKSODD. Pub. Country: Ukraine. Language: English. Summary Language: English; Ukrainian.

AB A highly metastatic to the liver gastric cancer cell line AZ-H was established by repeated intrasplenic injection of AZ-521 cells. In a Matrigel coated chamber AZ-H showed higher adhesiveness than AZ-521, and the invasiveness of AZ-H through Matrigel was significantly higher than that of AZ-521. Furthermore, AZ-H had higher metastatic potential to chicken liver than AZ-521. RT-PCR comparison of AZ-521 and AZZ-H in terms of the expression of 41 metastasis related genes showed that the expression of c-met, **VEGF-C** and integrin αvβ5 mRNAs and protein in AZ-H was higher than those in the parental cells AZ-521. Hepatocyte growth factor (HGF) expression was not found in parental AZ-521, but AZ-H showed both HGF and MET overexpression. Maspin mRNA expression in AZ-H was weaker than in AZ-521 cells. The remaining 36 genes showed no difference in the expression levels between AZ-H and AZ-521 cells. The incidence of liver metastasis in mice which had received intrasplenic infusion of anti-MET rabbit antibody treated AZ-H cells was significantly lower than that in mice, injected with normal rabbit IgG-treated AZ-H cells. Among 188 primary tumors 127 (68%) showed positive immunoreactivity for MET. Primary tumors of patients, who died of liver metastasis, exclusively showed MET immunoreaction. We conclude that liver metastasis of the AZ-H cells may be resulted from the simultaneous and concerted expression of **VEGF-C**, αvβ5 integrin, HGF and MET, and that invasion and proliferation of AZ-H cells in liver may be activated via the HGF/MET autocrine and paracrine **loop**.

L7 ANSWER 7 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:65164 Document No.: PREV200300065164. A paracrine **loop** in the vascular endothelial growth factor (**VEGF**) pathway triggers tumor angiogenesis and growth in patients with multiple myeloma. Ria, Roberto [Reprint Author]; Vacca, Angelo [Reprint Author]; Merchionne, Francesca [Reprint Author]; Semeraro, Fabrizio [Reprint Author]; Scavelli, Claudio [Reprint Author]; Pellegrino, Antonio [Reprint Author]; Dammacco, Franco [Reprint Author]. Section of Internal Medicine and Clinical Oncology, DIMO, University of Bari, Bari, Italy. Journal of Interferon and Cytokine Research, (2002) Vol. 22, No. Supplement 1, pp. S-66. print.
Meeting Info.: Joint Meeting of the International Society for Interferon and Cytokine Research, the International Cytokine Society, the Society for Leukocyte Biology, and the European Cytokine Society on Cytokines and Interferons. Turin, Italy. October 06-10, 2002. International Society for Interferon and Cytokine Research.
ISSN: 1079-9907 (ISSN print). Language: English.

L7 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
2001:545508 Document No. 135:132464 Cyclic peptide inhibitors of **VEGF**, **VEGF-C**, and **VEGF**-D, preparation methods, pharmaceutical compositions, and therapeutic use. Achen, Marc G.; Hughes, Richard A.; Stacker, Steven; Cendron, Angela (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2.

APPLICATION: WO 2001-US1533 20010118. PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.

AB The invention provides monomeric monocyclic peptide inhibitors and dimeric bicyclic peptide inhibitors based on exposed **loop** fragments of a growth factor protein, e.g. **loop** 1, **loop** 2 or **loop** 3 of **VEGF**-D, as well as methods of making them, pharmaceutical compns. containing them, and therapeutic methods of use.

L7 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN

2001:232264 Document No. 135:59293 c-JUN Gene Induction and AP-1 Activity Is Regulated by a JNK-Dependent Pathway in Hypoxic HepG2 Cells. Minet, E.; Michel, G.; Mottet, D.; Piret, J.-P.; Barbieux, A.; Raes, M.; Michiels, C. (Laboratoire de Biochimie et Biologie Cellulaire, FUNDP, Namur, 5000, Belg.). Experimental Cell Research, 265(1), 114-124 (English) 2001. CODEN: ECREAL. ISSN: 0014-4827. Publisher: Academic Press.

AB Hypoxia is an important pathophysiol. stress that occurs during blood vessel injuries and tumor growth. It is now well documented that hypoxia leads to the activation of several transcription factors which participate in the adaptive response of the cells to hypoxia. Among these transcription factors, AP-1 is rapidly activated by hypoxia and triggers bFGF, **VEGF**, and tyrosine hydroxylase gene expression. However, the mechanisms of AP-1 activation by hypoxia are not well understood. In this report, we studied the events leading to AP-1 activation in hypoxia. We found that c-jun protein accumulates in hypoxic HepG2 cells. This overexpression is concomitant with c-jun phosphorylation and JNK activation. Moreover, we showed that AP-1 is transcriptionally active. We also observed that AP-1 transcriptional activity is inhibited by a MEKK1 dominant neg. mutant. Moreover, the MEKK1 dominant neg. mutant as well as deletion of the AP-1 binding sites within the c-jun promoter inhibited the c-jun promoter activation by hypoxia. All together, these results indicate that, in hypoxic HepG2 cells, AP-1 is activated through a JNK-dependent pathway and that it is involved in the regulation of the c-jun promoter, inducing a pos. feedback **loop** on AP-1 activation via c-jun overexpression. (c) 2001 Academic Press.

L7 ANSWER 10 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

2001:312511 Document No.: PREV200100312511. **VEGF-C** signaling through Flt-4 (VEGFR3) mediates leukemic cell proliferation and survival. Choy, M. [Reprint author]; Dias, S. [Reprint author]; Alitalo, R.; Alitalo, K.; Rafii, S. [Reprint author]. Cornell U. Med. College, New York, NY, USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 502a-503a. print.

Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Recent findings have documented the relationship between leukemia and angiogenesis. In leukemia, increased bone marrow vessel density and vascular endothelial growth factor (**VEGF**) plasma levels correlate with poor prognosis. Leukemic cells secrete endothelial growth factors such as **VEGF** to enhance endothelial cell(EC) survival and proliferation while in turn ECs release growth factors such as GM-CSF to support leukemic cell growth. Given that other **VEGF** family members may play a role in leukemia biology, we speculated that **VEGF-C** may also modulate leukemic cell growth. **VEGF-C**, which binds VEGFR-2 (KDR) and VEGFR-3(Flt-4), was recently shown to be elaborated by subsets of leukemic cells. Similar to **VEGF**, **VEGF-C** increases EC migration and proliferation. However, in contrast to **VEGF**, it is expressed by various ECs including lymphatic EC and primary human umbilical vein EC (HUVEC) as well as certain solid and liquid tumors. Since the **VEGF-C** specific receptor, Flt-4, is expressed on primary leukemia cells and cell lines, we hypothesized that it may play a role in

leukemia cell growth and survival. In this study, the leukemia cell lines THP-1 and HEL were found to express functional Flt-4 receptors that phosphorylate upon stimulation by either **VEGF-C** or mutant **VEGF-C** (which only signals through Flt-4, but not KDR). Treatment with **VEGF-C** or its mutant in serum free conditions increased THP-1 and HEL proliferation by 20-30% over a 24-48 hr period. Additionally, both **VEGF-C** and its mutant enhanced THP-1 and HEL survival by 30-40%, as determined by Trypan blue exclusion and Annexin V staining. Its pro-survival effects were further demonstrated by an upregulation of the anti-apoptotic protein Bcl-2 in HEL and THP-1 cells following 24 hour serum-free treatment with either **VEGF-C** or its mutant. These results suggest that **VEGF-C** exerts both mitogenic and pro-survival effects on leukemic cells through its receptor Flt-4. Given that ECs as well as leukemic cells secrete **VEGF-C**, its production may support leukemic cell proliferation and survival through a Flt-4 mediated autocrine and/or paracrine mechanism. In this context, we demonstrate that leukemic cells produce pro-inflammatory cytokines such as IL-1 and TNF which increases **VEGF-C** production by HUVEC, generating a paracrine **loop** to support leukemia growth and survival. In turn, enhanced leukemia cell survival and proliferation may increase blood vessel density by elevating levels of leukemia-derived proangiogenic factors such as **VEGF** and FGF-2. These results identify the **VEGF-C**/Flt-4 pathway as a potential target for therapeutic intervention in subsets of human acute leukemias.

L7 ANSWER 11 OF 11 MEDLINE on STN DUPLICATE 7

1999438437. PubMed ID: 10506722. KDR activation in astrocytic neoplasms. Carroll R S; Zhang J; Bello L; Melnick M B; Maruyama T; McL Black P. (Neurosurgical Laboratories, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.) Cancer, (1999 Oct 1) 86 (7) 1335-41. Journal code: 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB BACKGROUND: The development of new capillary networks appears to be necessary for the growth of solid tumors. Tumor angiogenesis is believed to be mediated by soluble factors released from tumor cells that then act on endothelial cells in a paracrine manner. Vascular endothelial growth factor (**VEGF**) is a prime regulator of normal and tumor angiogenesis as well as vasculogenesis. **VEGF** is expressed in glioma cells and its receptors (Flt-1 and KDR) are expressed in the same gliomas. The two receptors are tyrosine kinases and have an extracellular domain containing seven immunoglobulin-like **loops** and a split tyrosine-kinase domain. KDR is a receptor for the various **VEGF** isoforms and for **VEGF-C**; Flt-1 is a receptor for the various isoforms. Studies suggest that the **VEGF** receptors are induced in endothelial cells during tumor angiogenesis. Stimulation of aortic endothelial cells results in receptor tyrosine phosphorylation (receptor activation). In this study the activation state of the KDR receptors was determined in low grade, anaplastic, and high grade gliomas. METHODS: A synthetic tyrosine phosphopeptide was used to raise an antibody that recognizes the phosphorylation state of tyrosine 1054/1059 in the KDR receptor. Western blot analysis was performed on 37 astrocytic neoplasms (7 low grade astrocytomas, 13 anaplastic astrocytomas, and 17 cases of glioblastoma multiforme). RESULTS: Immunoblotting with this antibody found that tyrosines 1054/1059 were phosphorylated constitutively within multiple fresh surgical specimens of glioblastomas (71%) and anaplastic gliomas (15%), but not in low grade gliomas. CONCLUSIONS: The findings of the current study strongly support the hypothesis that the onset of angiogenesis is an important event during the disease progression of gliomas.

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=> s VEGF
L8        46498 VEGF

=> s l8 and receptor binding site
L9           50 L8 AND RECEPTOR BINDING SITE

=> s l9 and structure
L10          29 L9 AND STRUCTURE

=> dup remove l10
PROCESSING COMPLETED FOR L10
L11          10 DUP REMOVE L10 (19 DUPLICATES REMOVED)

=> d l11 1-10 cbib abs

L11  ANSWER 1 OF 10  SCISEARCH  COPYRIGHT 2004 THOMSON ISI on STN
2003:782979   The Genuine Article (R) Number: 718UG. Structure and
      inhibitory effects on angiogenesis and tumor development of a new vascular
      endothelial growth inhibitor.  Zilberberg L; Shinkaruk S; Lequin O;
      Rousseau B; Hagedorn M; Costa F; Caronzolo D; Balke M; Canron X; Convert
      O; Lain G; Gionnet K; Goncalves M; Bayle M; Bello L; Chassaing G; Deleris
      G; Bikfalvi A (Reprint). Univ Bordeaux 1, INSERM, Mol Angiogenesis Lab, E
      0113, F-33405 Talence, France (Reprint); Univ Bordeaux 1, INSERM, Mol
      Angiogenesis Lab, F-33405 Talence, France; Univ Bordeaux 2, INSERM, U577,
      Grp Chim Bioorgan, F-33076 Bordeaux, France; Univ Paris 06, CNRS, UMR
      7613, F-75252 Paris, France; Univ Milan, Osped Maggiore Policlin, Ist Ric
      & Cura Carattere Sci, Dept Neurol Sci, I-20122 Milan, Italy. JOURNAL OF
      BIOLOGICAL CHEMISTRY (12 SEP 2003) Vol. 278, No. 37, pp. 35564-35573.
      Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC. 9650 ROCKVILLE
      PIKE, BETHESDA, MD 20814-3996 USA. ISSN: 0021-9258. Pub. country: France;
      Italy. Language: English.
      *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB       Blocking angiogenesis is an attractive strategy to inhibit tumor
      growth, invasion, and metastasis. We describe here the structure
      and the biological action of a new cyclic peptide derived from vascular
      endothelial growth factor ( VEGF). This 17-amino acid molecule
      designated cyclopeptidic vascular endothelial growth inhibitor
      (cyclo-VEGI, CBO-P11) encompasses residues 79 - 93 of VEGF which
      are involved in the interaction with VEGF receptor-2. In aqueous
      solution, cyclo-VEGI presents a propensity to adopt a helix conformation
      that was largely unexpected because only beta-sheet structures
      or random coil conformations have been observed for macrocyclic peptides.
      Cyclo-VEGI inhibits binding of iodinated VEGF(165) to
      endothelial cells, endothelial cells proliferation, migration, and
      signaling induced by VEGF(165). This peptide also exhibits
      anti-angiogenic activity in vivo on the differentiated chicken
      chorioallantoic membrane. Furthermore, cyclo-VEGI significantly blocks the
      growth of established intracranial glioma in nude and syngeneic mice and
      improves survival without side effects. Taken together, these results
      suggest that cyclo-VEGI is an attractive candidate for the development of
      novel angiogenesis inhibitor molecules useful for the treatment of cancer
      and other angiogenesis- related diseases.

L11  ANSWER 2 OF 10  SCISEARCH  COPYRIGHT 2004 THOMSON ISI on STN
2003:335969   The Genuine Article (R) Number: 666RD. A set of loop-1 and-3
      structures in the novel vascular endothelial growth factor (
      VEGF) family member, VEGF-ENZ-7, is essential for the
      activation of VEGFR-2 signaling.  Kiba A; Yabana N; Shibuya M (Reprint).
      Univ Tokyo, Inst Med Sci, Div Genet, Minato Ku, 4-6-1 Shirokane Dai, Tokyo
      1088639, Japan (Reprint); Univ Tokyo, Inst Med Sci, Div Genet, Minato Ku,
      Tokyo 1088639, Japan. JOURNAL OF BIOLOGICAL CHEMISTRY (11 APR 2003) Vol.
      278, No. 15, pp. 13453-13461. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR
      BIOLOGY INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA. ISSN:
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0021-9258. Pub. country: Japan. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The vascular endothelial growth factor (**VEGF**) family plays important roles in angiogenesis and vascular permeability. Novel members of the **VEGF** family encoded in the Orf virus genome, **VEGF**-E, function as potent angiogenic factors by specifically binding and activating VEGFR-2 (KDR). **VEGF**-E is about 45% homologous to **VEGF**-A at amino acid levels, however, the amino acid residues in **VEGF**-A crucial for the VEGFR-2-binding are not conserved in **VEGF**-E. To understand the molecular basis of the biological activity of **VEGF**-E, we have functionally mapped residues important for interaction of **VEGF**-E with VEGFR-2 by exchanging the domains between **VEGF**-ENZ-7 and PIGF, which binds only to VEGFR-1 (Flt-1). Exchange on the amino- and carboxyl-terminal regions had no suppressive effect on biological activity. However, exchange on either the loop-1 or -3 region of **VEGF**-ENZ-7 significantly reduced activities. On the other hand, introduction of the loop-1 and -3 of **VEGF**-ENZ-7 to placenta growth factor rescued the biological activities. The chimera between **VEGF**-A and **VEGF**-ENZ-7 gave essentially the same results. These findings strongly suggest that a common rule exists for VEGFR-2 ligands (**VEGF**-ENZ-7, and **VEGF**-A) that they build up the binding **structure** for VEGFR-2 through the appropriate interaction between loop-1 and -3 regions.

L11 ANSWER 3 OF 10 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:890732 The Genuine Article (R) Number: 607KU. Single-chain vascular endothelial growth factor variant with antagonist activity. Boesen T P; Soni B; Schwartz T W; Halkier T (Reprint). Maxygen ApS, Agern Alle 1, DK-2970 Horsholm, Denmark (Reprint); Maxygen ApS, DK-2970 Horsholm, Denmark; Univ Copenhagen, Dept Pharmacol, Mol Pharmacol Lab, DK-2200 Copenhagen N, Denmark. JOURNAL OF BIOLOGICAL CHEMISTRY (25 OCT 2002) Vol. 277, No. 43, pp. 40335-40341. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA. ISSN: 0021-9258. Pub. country: Denmark. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vascular endothelial growth factor is a specific endothelial cell mitogen that is essential for the formation of the vascular system but in the adult individual is involved in several pathological conditions, including cancer. It is a homodimeric protein that activates its receptor by binding two receptor molecules and inducing dimerization. By mixing two vascular endothelial growth factor monomers, each with different substitutions, heterodimers with only one active **receptor binding site** have previously been prepared. These heterodimers bind the receptor molecule but are unable to induce dimerization and activation. However, preparation of heterodimers is cumbersome, involving separate expression of different monomers, refolding the mixture, and separating heterodimers from homodimers. Here we show that a fully functional ligand can efficiently be expressed as a single protein chain containing two monomers. Single-chain vascular endothelial growth factor is functionally equivalent to the wild-type protein. By monomer-specific mutagenesis, one **receptor binding site** was altered. This variant competitively and specifically antagonizes the mitogenic effect of the wild-type protein on endothelial cells. The results obtained with the single-chain antagonist show the feasibility of the single-chain approach in directing alterations to single specific regions in natural homodimeric proteins that would be impossible to target in other ways.

L11 ANSWER 4 OF 10 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:885224 The Genuine Article (R) Number: 607KZ. Characterization of the vascular endothelial growth factor-receptor interaction and determination of the recombinant protein by an optical receptor sensor. von Tiedemann B; Bilitewski U (Reprint). German Res Ctr Biotechnol Ltd, GBF, Div Biochem

Engn, Mascheroder Weg 1, D-38124 Braunschweig, Germany (Reprint); German Res Ctr Biotechnol Ltd, GBF, Div Biochem Engn, D-38124 Braunschweig, Germany. BIOSENSORS & BIOELECTRONICS (DEC 2002) Vol. 17, No. 11-12, Sp. iss. SI, pp. 983-991. Publisher: ELSEVIER ADVANCED TECHNOLOGY. OXFORD FULFILLMENT CENTRE THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND. ISSN: 0956-5663. Pub. country: Germany. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vascular endothelial growth factor (**VEGF**) is one of the most important factors controlling angiogenesis. It is a homodimeric glycoprotein belonging to the family of cysteine-knot proteins. The biological activity is transduced via membrane-spanning receptors of the tyrosine kinase receptor family. Each biologically active **VEGF** has two **receptor binding sites** leading to receptor dimerization as first step following ligand binding. The ligand-binding site of the receptor is localized on extracellular Ig-like domains. The extracellular part of the receptor Flt-1 (VEGFR-1) was expressed as soluble protein and was used as receptor in an optical affinity sensor system (BIAcore). Suitable conditions allowed the determination of the association and dissociation rate constants as k(a) = 4 +/- 1.2 x 10(6) M-1 s(-1) and k(d) = 3 +/- 0.8 x 10(-5) s(-1), respectively, leading to an affinity constant of K-D = 7.5 +/- 3 pM, which is within the range published already from other investigations and methods. Increasing receptor loadings of the sensor surface decreased the binding efficiency, as the ratio of bound **VEGF**-molecules to theoretically available binding sites increased from 1:1.5 to 1:2.6. Increasing the surface loading further, allowed the establishment of a quantitative assay with the analytical performance being influenced by the receptor loading and the contact time between sample and immobilized receptor, i.e. sample volume. This assay was used for **VEGF** determination during the cultivation of a recombinant Pichia pastoris strain.

L11 ANSWER 5 OF 10 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 1

2000:731118 The Genuine Article (R) Number: 356JH. Receptor-selective variants of human vascular endothelial growth factor - Generation and characterization. Li B; Fuh G; Meng G; Xin X H; Gerritsen M E; Cunningham B; deVos A M (Reprint). GENENTECH INC, DEPT PROT ENGN, 1 DNA WAY, S SAN FRANCISCO, CA 94080 (Reprint); GENENTECH INC, DEPT PROT ENGN, S SAN FRANCISCO, CA 94080; GENENTECH INC, DEPT BIOANALYT TECHNOL, S SAN FRANCISCO, CA 94080; GENENTECH INC, DEPT CARDIOVASC RES, S SAN FRANCISCO, CA 94080. JOURNAL OF BIOLOGICAL CHEMISTRY (22 SEP 2000) Vol. 275, No. 38, pp. 29823-29828. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0021-9258. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Vascular endothelial growth factor (**VEGF**) is a pleiotropic factor that exerts a multitude of biological effects through its interaction with two receptor tyrosine kinases, fms-like tyrosine kinase (Flt-1) or **VEGF** receptor 1 and kinase insert domain-containing receptor (KDR) or **VEGF** receptor 2. Whereas it is commonly accepted that KDR is responsible for the proliferative activities of **VEGF**, considerable controversy and uncertainty exist about the role of the individual receptors in eliciting many of the other effects. Based on a comprehensive mutational analysis of the **receptor-binding site** of **VEGF**, an Flt-1-selective variant was created containing four substitutions from the wild-type protein. This variant bound with wild-type affinity to Flt-1, was at least 470-fold reduced in binding to KDR, and had no activity in cell-based assays measuring autophosphorylation of KDR or proliferation of primary human vascular endothelial cells. Using a competitive phage display strategy, two KDR-selective variants were discovered with three and four changes from wild-type, respectively. Both variants had approximately

wild-type affinity for KDR, were about 2000-fold reduced in binding to Flt-1, and showed activity comparable with the wild-type protein in KDR autophosphorylation and endothelial cell proliferation assays. These variants will serve as useful reagents in elucidating the roles of Flt-1 and KDR.

L11 ANSWER 6 OF 10 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 2

1999018836 EMBASE Novel peptides selected to bind vascular endothelial growth factor target the **receptor-binding site.**
Fairbrother W.J.; Christinger H.W.; Cochran A.G.; Fuh G.; Keenan C.J.; Quan C.; Shriver S.K.; Tom J.Y.K.; Wells J.A.; Cunningham B.C.. B.C. Cunningham, Protein Engg./Bioorganic Chem. Dept., Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, United States. bcc@sunesis-pharma.com.
Biochemistry 37/51 (17754-17764) 22 Dec 1998.
Refs: 53.
ISSN: 0006-2960. CODEN: BICHAW. Pub. Country: United States. Language: English. Summary Language: English.

AB Peptides that inhibit binding of vascular endothelial growth factor (**VEGF**) to its receptors, KDR and Flt-1, have been produced using phage display. Libraries of short disulfide-constrained peptides yielded three distinct classes of peptides that bind to the receptor-binding domain of **VEGF** with micromolar affinities. The highest affinity peptide was also shown to antagonize **VEGF**-induced proliferation of primary human umbilical vascular endothelial cells. The peptides bind to a region of **VEGF** known to contain the contact surface for Flt-1 and the functional determinants for KDR binding. This suggests that the receptor-binding region of **VEGF** is a binding 'hot spot' that is readily targeted by selected peptides and supports earlier assertions that phage-derived peptides frequently target protein-protein interaction sites. Such peptides may lead to the development of pharmacologically useful **VEGF** antagonists.

L11 ANSWER 7 OF 10 MEDLINE on STN DUPLICATE 3

1998225203. PubMed ID: 9556609. Requirements for binding and signaling of the kinase domain receptor for vascular endothelial growth factor. Fuh G; Li B; Crowley C; Cunningham B; Wells J A. (Department of Protein Engineering, Genentech, Inc., South San Francisco, California 94080, USA.) Journal of biological chemistry, (1998 May 1) 273 (18) 11197-204.
Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States.
Language: English.

AB Vascular endothelial growth factor (**VEGF**) is a dimeric hormone that controls much of vascular development through binding and activation of its kinase domain receptor (KDR). We produced analogs of **VEGF** that show it has two **receptor-binding sites** which are located near the poles of the dimer and straddle the interface between subunits. Deletion experiments in KDR indicate that of the seven IgG-like domains in the extracellular domain, only domains 2-3 are needed for tight binding of **VEGF**. Monomeric forms of the extracellular domain of KDR bind approximately 100 times weaker than dimeric forms showing a strong avidity component for binding of **VEGF** to predimerized forms of the receptor. Based upon these **structure** -function studies and a mechanism in which receptor dimerization is critical for signaling, we constructed a receptor antagonist in the form of a heterodimer of **VEGF** that contained one functional and one non-functional site. These studies establish a functional foundation for the design of **VEGF** analogs, mimics, and antagonists.

L11 ANSWER 8 OF 10 MEDLINE on STN DUPLICATE 4

1998284306. PubMed ID: 9621286. Receptors of vascular endothelial growth factor/vascular permeability factor (**VEGF**/VPF) in fetal and adult human kidney: localization and [125I]**VEGF** binding sites.
Simon M; Rockl W; Hornig C; Grone E F; Theis H; Weich H A; Fuchs E; Yayon

A; Grone H J. (Institute of Pathology, Philipps University, Marburg, Germany.) Journal of the American Society of Nephrology : JASN, (1998 Jun) 9 (6) 1032-44. Journal code: 9013836. ISSN: 1046-6673. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (**VEGF**) has an important function in renal vascular ontogenesis and is constitutively expressed in podocytes of the adult kidney. The ability of **VEGF** to be chemotactic for monocytes and to increase the activity of collagenase and plasminogen activator may have implications for renal development and renal disease. In humans, the cellular actions of **VEGF** depend on binding to two specific receptors: Flt-1 and KDR. The aims of this study were: (1) to localize **VEGF** receptor proteins in human renal ontogenesis; (2) to quantify **VEGF** binding in human fetal and adult kidney; and (3) to dissect the binding into its two known components: the KDR and Flt-1 receptors. The latter aim was achieved by competitive binding of **VEGF** and placenta growth factor-2, which only binds to Flt-1. Quantification of 125I-**VEGF** binding sites was performed by autoradiography and computerized densitometry. By double-label immunohistochemistry, **VEGF** receptor proteins were localized solely to endothelial cells of preglomerular vessels, glomeruli, and postglomerular vessels. In developing glomeruli, **VEGF** receptor protein appeared as soon as endothelial cells were positive for von Willebrand factor. Specific 125I-**VEGF** binding could be localized to renal arteries and veins, glomeruli, and the tubulointerstitial capillary network in different developmental stages. Affinity (Kd) of adult (aK) and fetal (fK) kidneys was: Kd: glomeruli 38.6 +/- 11.2 (aK, n = 5), 36.3 +/- 7.1 (fK, n = 5); cortical tubulointerstitium 19.4 +/- 2.6 (aK, n = 5), 11.6 +/- 7.0 (fK, n = 5) pmol. Placenta growth factor-2 displaced **VEGF** binding in all renal **structures** by approximately 60%. **VEGF** receptor proteins thus were found only in renal endothelial cells. A coexpression of both **VEGF** binding sites could be shown, with Flt-1 demonstrating the most abundant **VEGF receptor binding sites** in the kidney. These studies support the hypothesis of a function for **VEGF** in adult kidney that is independent of angiogenesis.

L11 ANSWER 9 OF 10 MEDLINE on STN DUPLICATE 5

97352774. PubMed ID: 9207067. Vascular endothelial growth factor: crystal **structure** and functional mapping of the kinase domain **receptor binding site**. Muller Y A; Li B; Christinger H W; Wells J A; Cunningham B C; de Vos A M. (Genentech, Inc., Department of Protein Engineering, 460 Point San Bruno Boulevard, South San Francisco, CA 94080, USA.) Proceedings of the National Academy of Sciences of the United States of America, (1997 Jul 8) 94 (14) 7192-7. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (**VEGF**) is a homodimeric member of the cystine knot family of growth factors, with limited sequence homology to platelet-derived growth factor (PDGF) and transforming growth factor beta2 (TGF-beta). We have determined its crystal **structure** at a resolution of 2.5 A, and identified its kinase domain receptor (KDR) binding site using mutational analysis. Overall, the **VEGF** monomer resembles that of PDGF, but its N-terminal segment is helical rather than extended. The dimerization mode of **VEGF** is similar to that of PDGF and very different from that of TGF-beta. Mutational analysis of **VEGF** reveals that symmetrical binding sites for KDR are located at each pole of the **VEGF** homodimer. Each site contains two functional "hot spots" composed of binding determinants presented across the subunit interface. The two most important determinants are located within the largest hot spot on a short, three-stranded sheet that is conserved in PDGF and TGF-beta. Functional analysis of the binding epitopes for two receptor-blocking antibodies

reveal different binding determinants near each of the KDR binding hot spots.

L11 ANSWER 10 OF 10 MEDLINE on STN DUPLICATE 6
1998035455. PubMed ID: 9351807. The crystal **structure** of vascular endothelial growth factor (**VEGF**) refined to 1.93 A resolution: multiple copy flexibility and receptor binding. Muller Y A; Christinger H W; Keyt B A; de Vos A M. (Department of Protein Engineering, Genentech, Inc., South San Francisco, CA 94080, USA.) Structure (London, England), (1997 Oct 15) 5 (10) 1325-38. Journal code: 9418985. ISSN: 0969-2126. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Vascular endothelial growth factor (**VEGF**) is an endothelial cell-specific angiogenic and vasculogenic mitogen. **VEGF** also plays a role in pathogenic vascularization which is associated with a number of clinical disorders, including cancer and rheumatoid arthritis. The development of **VEGF** antagonists, which prevent the interaction of **VEGF** with its receptor, may be important for the treatment of such disorders. **VEGF** is a homodimeric member of the cystine knot growth factor superfamily, showing greatest similarity to platelet-derived growth factor (PDGF). **VEGF** binds to two different tyrosine kinase receptors, kinase domain receptor (KDR) and Fms-like tyrosine kinase 1 (Flt-1), and a number of **VEGF** homologs are known with distinct patterns of specificity for these same receptors. The **structure** of **VEGF** will help define the location of the **receptor-binding site**, and shed light on the differences in specificity and cross-reactivity among the **VEGF** homologs. RESULTS: We have determined the crystal **structure** of the receptor-binding domain of **VEGF** at 1.93 A resolution in a triclinic space group containing eight monomers in the asymmetric unit. Superposition of the eight copies of **VEGF** shows that the beta-sheet core regions of the monomers are very similar, with slightly greater differences in most loop regions. For one loop, the different copies represent different snapshots of a concerted motion. Mutagenesis mapping shows that this loop is part of the **receptor-binding site** of **VEGF**. CONCLUSIONS: A comparison of the eight independent copies of **VEGF** in the asymmetric unit indicates the conformational space sampled by the protein in solution; the root mean square differences observed are similar to those seen in ensembles of the highest precision NMR **structures**. Mapping the receptor-binding determinants on a multiple sequence alignment of **VEGF** homologs, suggests the differences in specificity towards KDR and Flt-1 may derive from both sequence variation and changes in the flexibility of binding loops. The **structure** can also be used to predict possible receptor-binding determinants for related cystine knot growth factors, such as PDGF.

=> s VEGF receptor binding domain
L12 12 VEGF RECEPTOR BINDING DOMAIN

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13 6 DUP REMOVE L12 (6 DUPLICATES REMOVED)

=> d l13 1-6 cbib abs

L13 ANSWER 1 OF 6 EMBASE
on STN DUPLICATE 1
2003189004 EMBASE NMR structural analysis of vascular endothelial growth factor in complex with a phage-derived peptide antagonist. Pan B.; Fairbrother W.J.. W.J. Fairbrother, Department of Protein Engineering, Genentech, Inc., South San Francisco, CA 94080, United States. fairbro@gene.com. Spectroscopy 17/2-3 (169-181) 2003.

Refs: 57.
ISSN: 0712-4813. CODEN: SPIJDZ. Pub. Country: Netherlands. Language: English. Summary Language: English.

AB Vascular endothelial growth factor (VEGF) is a covalently linked homodimeric protein that functions as an endothelial cell-specific mitogen, and is an important mediator of pathological angiogenesis. Phage display has been used to select three different classes of novel disulfide-constrained peptides that bind to VEGF and disrupt receptor binding with IC(50) values between 0.2-10 μM. Mapping of peptide induced nuclear magnetic resonance (NMR) chemical shift changes shows that they target a region of the **VEGF receptor-binding domain** that overlaps with the contact surfaces of the receptors, Flt-1 and KDR. The structure of one of these 28-kDa VEGF/peptide complexes was determined by NMR spectroscopy. The structure is based on a total of 4416 internuclear distance and dihedral angle restraints derived from data obtained using samples of the complex containing either (13)C/(15)N-labeled peptide or protein. Incorporation of residual dipolar coupling restraints improved both the precision and accuracy of the structure (as judged by comparison with crystal structures of VEGF). Comparison with the structure of a different VEGF/peptide complex reveals different peptide binding modes that each resemble those of natural protein ligands (an anti-VEGF antibody and the VEGF-receptor Flt-1). Prospects for the development of small-molecule antagonists of VEGF, based on the VEGF-bound peptide structures, are discussed.

L13 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

2003:932900 Inhibition of vascular endothelia growth factor receptor binding domain-GraB to KDR/flt-1 prositive endothelial proliferation in vitro and angiogenesis in vivo. Li, Xianmao; Zeng, Weisen; Zhang, Yali; Liu, Xiaoqing (Nanfang Hospital, First Military Medical University, Guangzhou, Guangdong Province, 510515, Peop. Rep. China). Disi Junyi Daxue Xuebao, 23(21), 1929-1932 (Chinese) 2002. CODEN: DJDXEG. ISSN: 1000-2790. Publisher: Disi Junyi Daxue Xuebao Bianjibu.

AB An inducible system for expression of **VEGF receptor-binding domain**-GraB in E. coli on the basis of expressive specifity of VEGF receptor on the vascular endothelial of tumor and of the effect that GraB induces cell apoptosis was developed. The biol. function of **VEGF receptor-binding domain**-GraB was studied for the purpose of antiangiogenesis research. After GraB cDNA and hVEGF receptor-binding domain cDNA were amplified by RT-PCR via extracting lymphocyte total RNA and LoVo cell total RNA resp., the fusion gene was inserted into E. coli expression vector pTrcHis2A. The prokaryotic expression plasmid PtrcHis2A/VEGFD-GraB was constructed and transformed into TOP10F. After 8 h of IPTG induction, the **VEGF receptor-binding domain**-GraB was expressed to 15% of total proteins. Western blot assay proved the expressed protein to be of good antigenicity and high specificity. The recombinant protein purified by affinity chromatog. was proved to inhibit ECV303 proliferation and destroy neovascularization of the chick chorioallantoic membrance. **VEGF receptor-binding domain**-GraB fusion protein may be a potent inhibitor of tumor angiogenesis and metastasis.

L13 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 2

2002132078. PubMed ID: 11866530. Solution structure of a phage-derived peptide antagonist in complex with vascular endothelial growth factor. Pan Borlan; Li Bing; Russell Stephen J; Tom Jeffrey Y K; Cochran Andrea G; Fairbrother Wayne J. (Department of Protein Engineering, Genentech Inc., South San Francisco, CA 94080, USA.) Journal of molecular biology, (2002 Feb 22) 316 (3) 769-87. Journal code: 2985088R. ISSN: 0022-2836. Pub. country: England: United Kingdom. Language: English.

AB Vascular endothelial growth factor (VEGF) is a potent endothelial cell-specific mediator of angiogenesis and vasculogenesis. VEGF is

involved pathologically in cancer, proliferative retinopathy and rheumatoid arthritis, and as such represents an important therapeutic target. Three classes of disulfide-constrained peptides that antagonize binding of the VEGF dimer to its receptors, KDR and Flt-1, were identified previously using phage display methods. NMR studies of a representative peptide from the most potent class of these peptide antagonists, v107 (GGNECDAIRMWEWECFERL), were undertaken to characterize its interactions with VEGF. v107 has no defined structure free in solution, but binding to VEGF induces folding of the peptide. The solution structure of the **VEGF receptor-binding domain**-v107 complex was determined using 3940 (1970 per VEGF monomer) internuclear distance and 476 (238 per VEGF monomer) dihedral angle restraints derived from NMR data obtained using samples containing either (13)C/(15)N-labeled protein plus excess unlabeled peptide or (13)C/(15)N-labeled peptide plus excess unlabeled protein. Residual dipolar coupling restraints supplemented the structure determination of the complex and were found to increase significantly both the global precision of VEGF in the complex and the agreement with available crystal structures of VEGF. The calculated ensemble of structures is of high precision and is in excellent agreement with the experimental restraints. v107 has a turn-helix conformation with hydrophobic residues partitioned to one face of the peptide and polar or charged residues at the other face. Contacts between two v107 peptides and the VEGF dimer are mediated by primarily hydrophobic side-chain interactions. The v107-binding site on VEGF overlaps partially with the binding site of KDR and is similar to that for domain 2 of Flt-1. The structure of the VEGF-v107 complex provides new insight into how binding to VEGF can be achieved that may be useful for the design of small molecule antagonists.

L13 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
2002:210837 Document No. 136:335353 Letter to the editor: 1H, 13C, and 15N resonance assignment of the vascular endothelial growth factor receptor-binding domain in complex with a receptor-blocking peptide. Pan, Borlan; Fairbrother, Wayne J. (Department of Protein Engineering, Genentech, Inc., South San Francisco, CA, 94080, USA). Journal of Biomolecular NMR, 22(2), 189-190 (English) 2002. CODEN: JBNME9. ISSN: 0925-2738. Publisher: Kluwer Academic Publishers.
AB Three classes of disulfide-constrained peptides that block binding of VEGF to its receptors were identified recently using phage-display methods. As a first step in characterizing the complex between VEGF and this class of phage derived peptide antagonists by NMR, we report here nearly complete assignments for VEGF11-109 in complex with peptide v107. Comparison with backbone assignments reported previously for free VEGF11-109 allows for identification of the peptide-binding site via quant. chemical shift mapping.

L13 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
1997:671526 Document No. 127:326679 1H, 13C, and 15N backbone assignment and secondary structure of the receptor-binding domain of vascular endothelial growth factor. Fairbrother, Wayne J.; Champe, Mark A.; Christinger, Hans W.; Keyt, Bruce A.; Starovasnik, Melissa A. (Department of Protein Engineering, Genentech Inc., South San Francisco, CA, 94080, USA). Protein Science, 6(10), 2250-2260 (English) 1997. CODEN: PRCIEI. ISSN: 0961-8368. Publisher: Cambridge University Press.
AB Nearly complete sequence-specific 1H, 13C, and 15N resonance assignments are reported for the backbone atoms of the receptor-binding domain of vascular endothelial growth factor (VEGF), a 23-kDa homodimeric protein that is a major regulator of both normal and pathol. angiogenesis. The assignment strategy relied on the use of seven 3D triple-resonance expts. [HN(CO)CA, HNCA, HNCO, (HCA)CONH, HN(COCA)HA, HN(CA)HA, and CBCA(CO)NH] and a 3D 15N-TOCSY-HSQC experiment recorded on a 0.5 mM (12 mg/mL) sample at 500 MHz, pH 7.0, 45°. Under these conditions, 15N relaxation data show that the protein has a rotational correlation time of 15.0 ns.

Despite this unusually long correlation time, assignments were obtained for 94 of the 99 residues; 8 residues lack amide 1H and 15N assignments, presumably due to rapid exchange of the amide 1H with solvent under the exptl. conditions used. The secondary structure of the protein was deduced from the chemical shift indexes of the 1Hα, 13Cα, 13Cβ, and 13CO nuclei, and from anal. of backbone NOEs observed in a 3D 15N-NOESY-HSQC spectrum. Two helixes and a significant amount of β-sheet structure were identified, in general agreement with the secondary structure found in a recently determined crystal structure of a similar VEGF construct.

L13 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
1996:730251 Document No. 126:84767 Crystallization of the receptor binding domain of vascular endothelial growth factor. Christinger, Hans W.; Muller, Yves A.; Berleau, Lea T.; Keyt, Bruce A.; Cunningham, Brian C.; Ferrara, Napoleone; de Vos, Abraham M. (Departments of Protein Eng. Cardiovas. Res., Genentech, Inc., S. San Francisco, CA, USA). Proteins: Structure, Function, and Genetics, 26(3), 353-357 (English) 1996. CODEN: PSFGEY. ISSN: 0887-3585. Publisher: Wiley-Liss.

AB Vascular endothelial growth factor (VEGF) is a potent angiogenic factor with a unique specificity for vascular endothelial cells. In addition to its role in vasculogenesis and embryonic angiogenesis, VEGF is implicated in pathol. neovascularization associated with tumors and diabetic retinopathy. Four different constructs of a short variant of VEGF sufficient for receptor binding were overexpressed in Escherichia coli, refolded, purified, and crystallized in five different space groups. In order to facilitate the production of heavy atom derivs., single cysteine mutants were designed based on the crystal structure of platelet-derived growth factor. A construct consisting of residues 8 to 109 was crystallized in space group P21, with cell parameters α = 55.6 Å, b = 60.4 Å, c = 77.7 Å, β = 90.0°, and four monomers in the asym. unit. Native and derivative data were collected for two of the cysteine mutants as well as for wild-type VEGF.

```
=> s VEGF peptide
L14          87 VEGF PEPTIDE

=> s l14 and monoclyclic
L15           0 L14 AND MONOCLYCLIC

=> s monocyclic peptide
L16          76 MONOCYCLIC PEPTIDE

=> s l16 and VEGF
L17           1 L16 AND VEGF

=> d l17 cbib abs

L17 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
2001:545508 Document No. 135:132464 Cyclic peptide inhibitors of
     VEGF, VEGF-C, and VEGF-D, preparation methods,
     pharmaceutical compositions, and therapeutic use. Achen, Marc G.; Hughes,
     Richard A.; Stacker, Steven; Cendron, Angela (Ludwig Institute for Cancer
     Research, USA). PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp.
     DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ,
     CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
     HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
     LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG,
     SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY,
     KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE,
     DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN,
     TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1533
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20010118. PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.
AB The invention provides monomeric **monocyclic peptide** inhibitors and dimeric bicyclic peptide inhibitors based on exposed loop fragments of a growth factor protein, e.g. loop 1, loop 2 or loop 3 of **VEGF**-D, as well as methods of making them, pharmaceutical compns. containing them, and therapeutic methods of use.

=> d his

(FILE 'HOME' ENTERED AT 11:08:46 ON 11 MAR 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:09:00 ON 11 MAR 2004

```
L1             0 S VEGF BINDING LOOP
L2         46498 S VEGF
L3             6 S L2 AND BINDING LOOP
L4             3 DUP REMOVE L3 (3 DUPLICATES REMOVED)
L5          1681 S L2 AND VEGF-C
L6            36 S L5 AND LOOP
L7            11 DUP REMOVE L6 (25 DUPLICATES REMOVED)
L8         46498 S VEGF
L9            50 S L8 AND RECEPTOR BINDING SITE
L10           29 S L9 AND STRUCTURE
L11           10 DUP REMOVE L10 (19 DUPLICATES REMOVED)
L12           12 S VEGF RECEPTOR BINDING DOMAIN
L13            6 DUP REMOVE L12 (6 DUPLICATES REMOVED)
L14           87 S VEGF PEPTIDE
L15            0 S L14 AND MONOCLYCLIC
L16           76 S MONOCYCLIC PEPTIDE
L17            1 S L16 AND VEGF

=> s l8 and binding loop
L18            6 L8 AND BINDING LOOP

=> dup remove l18
PROCESSING COMPLETED FOR L18
L19            3 DUP REMOVE L18 (3 DUPLICATES REMOVED)

=> d l19 1-3 cbib abs
```

L19 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
2003:275911 Document No. 139:95567 A set of loop-1 and -3 structures in the novel vascular endothelial growth factor (**VEGF**) family member, **VEGF**-ENZ-7, is essential for the activation of VEGFR-2 signaling.
Kiba, Atsushi; Yabana, Naoyuki; Shibuya, Masabumi (Institute of Medical Science, Division of Genetics, University of Tokyo, 4-6-1 Shirokane-dai, Minato-ku, Tokyo, 108-8639, Japan). Journal of Biological Chemistry, 278(15), 13453-13461 (English) 2003. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.
AB The vascular endothelial growth factor (**VEGF**) family plays important roles in angiogenesis and vascular permeability. Novel members of the **VEGF** family encoded in the Orf virus genome, **VEGF** -E, function as potent angiogenic factors by specifically binding and activating VEGFR-2 (KDR). **VEGF**-E is about 45% homologous to **VEGF**-A at amino acid levels, however, the amino acid residues in **VEGF**-A crucial for the VEGFR-2-binding are not conserved in **VEGF**-E. To understand the mol. basis of the biol. activity of **VEGF**-E, the authors have functionally mapped residues important for interaction of **VEGF**-E with VEGFR-2 by exchanging the domains between **VEGF**-ENZ-7 and PlGF, which binds only to VEGFR-1 (Flt-1). Exchange on the amino- and C-terminal regions had no suppressive effect on biol. activity. However, exchange on either the loop-1 or -3

region of **VEGF**-ENZ-7 significantly reduced activities. Introduction of the loop-1 and -3 of **VEGF**-ENZ-7 to placenta growth factor rescued the biol. activities. The chimera between **VEGF**-A and **VEGF**-ENZ-7 gave essentially the same results. These findings strongly suggest that a common rule exists for VEGFR-2 ligands (**VEGF**-ENZ-7 and **VEGF**-A) that they build up the binding structure for VEGFR-2 through the appropriate interaction between loop-1 and -3 regions.

L19 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 1

1998035455. PubMed ID: 9351807. The crystal structure of vascular endothelial growth factor (**VEGF**) refined to 1.93 A resolution: multiple copy flexibility and receptor binding. Muller Y A; Christinger H W; Keyt B A; de Vos A M. (Department of Protein Engineering, Genentech, Inc., South San Francisco, CA 94080, USA.) Structure (London, England), (1997 Oct 15) 5 (10) 1325-38. Journal code: 9418985. ISSN: 0969-2126. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Vascular endothelial growth factor (**VEGF**) is an endothelial cell-specific angiogenic and vasculogenic mitogen. **VEGF** also plays a role in pathogenic vascularization which is associated with a number of clinical disorders, including cancer and rheumatoid arthritis. The development of **VEGF** antagonists, which prevent the interaction of **VEGF** with its receptor, may be important for the treatment of such disorders. **VEGF** is a homodimeric member of the cystine knot growth factor superfamily, showing greatest similarity to platelet-derived growth factor (PDGF). **VEGF** binds to two different tyrosine kinase receptors, kinase domain receptor (KDR) and Fms-like tyrosine kinase 1 (Flt-1), and a number of **VEGF** homologs are known with distinct patterns of specificity for these same receptors. The structure of **VEGF** will help define the location of the receptor-binding site, and shed light on the differences in specificity and cross-reactivity among the **VEGF** homologs. RESULTS: We have determined the crystal structure of the receptor-binding domain of **VEGF** at 1.93 A resolution in a triclinic space group containing eight monomers in the asymmetric unit. Superposition of the eight copies of **VEGF** shows that the beta-sheet core regions of the monomers are very similar, with slightly greater differences in most loop regions. For one loop, the different copies represent different snapshots of a concerted motion. Mutagenesis mapping shows that this loop is part of the receptor-binding site of **VEGF**. CONCLUSIONS: A comparison of the eight independent copies of **VEGF** in the asymmetric unit indicates the conformational space sampled by the protein in solution; the root mean square differences observed are similar to those seen in ensembles of the highest precision NMR structures. Mapping the receptor-binding determinants on a multiple sequence alignment of **VEGF** homologs, suggests the differences in specificity towards KDR and Flt-1 may derive from both sequence variation and changes in the flexibility of **binding loops**. The structure can also be used to predict possible receptor-binding determinants for related cystine knot growth factors, such as PDGF.

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

1996:548535 Document No. 125:215688 Ribozymes with RNA protein-binding site and ribozyme domain loop conformation. Burke, John M.; Sargueil, Bruno (University of Vermont and State Agricultural College, USA). PCT Int. Appl. WO 9621730 A2 19960718, 55 pp. DESIGNATED STATES: W: AU, CA, JP, MX; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1995-US16882 19951227. PRIORITY: US 1995-371986 19950113.

AB This invention includes ribozymes having a ligand-binding site formed as a double-stranded RNA and a single-stranded loop. The ribozymes have enzymic activity to cleave and/or ligate themselves or sep. RNA mols. Especially ribozyme protein-binding sites are studied. Recombinant ribozymes